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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/527,821	03/15/2005	Frans Eduard Janssens	JANS-0077	4572

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EXAMINER	
JARRELL, NOBLE E	
ART UNIT	**PAPER NUMBER**
1624	

MAIL DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/527,821	JANSSENS ET AL.	
	Examiner	Art Unit	
	Noble Jarrell	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 August 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-4 and 6-16* is/are pending in the application.

4a) Of the above claim(s) *1 and 10-13* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *2,3,6-9,16* is/are rejected.

7)☒ Claim(s) *14 and 15* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *15 March 2005*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Applicant's election with traverse of group I in the reply filed on 8/2/2007 is acknowledged. The traversal is on the ground(s) that searching all possibilities of claim 1 does not constitute a search burden. This is not found persuasive because they are a total of 7 other combinations of variables m, n, and p, other than the instance when they are all one. Each of these other combinations creates another core structure formed by the three rings. Claim 1 will be viewed in light of claim 2, because the only way to understand claim 2 is through analysis of claim 1.

The requirement is still deemed proper and is therefore made FINAL.

Specification

2. Applicant is reminded of the proper language and format for an abstract of the disclosure.

The abstract should be in narrative form and generally limited to a single paragraph on a separate sheet within the range of 50 to 150 words. It is important that the abstract not exceed 150 words in length since the space provided for the abstract on the computer tape used by the printer is limited. The form and legal phraseology often used in patent claims, such as "means" and "said," should be avoided. The abstract should describe the disclosure sufficiently to assist readers in deciding whether there is a need for consulting the full patent text for details.

The language should be clear and concise and should not repeat information given in the title. It should avoid using phrases which can be implied, such as, "The disclosure . concerns," "The disclosure defined by this invention," "The disclosure describes," etc.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 2-3 and 8-9 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for preparation of final compounds depicted in pages 34-44 and compounds in tables 1-5, does not reasonably provide enablement for every possible compound envisaged by claim 2, as well as their prodrugs. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Applicants are limited to chemical compounds that fall under the rules for electrophilic aromatic substitution. These rules are described by Smith (*March's Advanced Organic Chemistry*, **2001**, pages 681-690). Many of these compounds are prepared. However, the manner in which the claims are drawn can refer to invalid substitution patterns on a phenyl or naphthalene ring. When variable R^2 is an unsaturated ring, groups attached to the ring determine the pattern of electrophilic aromatic substitution. In the case of these claims, the substitution pattern of the (hetero)aromatic ring is determined by the group that couples with the nitrogen of piperidine ring. When the group is a C(O)-halogen group, as used in the syntheses, substituents can only be *ortho* (*o*) or *para* (*p*). If the group that attaches to the piperidine is OC(O)-Halogen, SC(O)Halogen, NHC(O)Halogen, or N(Alkyl)C(O)Halogen, the substitution occurs at the same positions. All of these groups are electron-donating, and in electrophilic aromatic substitution, substitution occurs at the *o* and *p* positions of the ring. Therefore, applicants are not enabled for compounds where the groups are *meta* to the carbonyl group. Applicants have also not prepared any prodrugs of the parent compounds.

> The factors to be considered in determining whether a disclosure meets the enablement requirements of 35 U.S.C. 112, first paragraph, have been described in *In re Wands*, 858 F.2d 731, 8 USPQ2d 1400 (Fed. Cir., 1988). The court in Wands states, "Enablement is not precluded by the necessity for some experimentation, such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue', not 'experimentation'" (*Wands*, 8 USPQ2sd 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a

single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations" (*Wands*, 8 USPQ2d 1404). Among these factors are: (1) the nature of the invention; (2) the breadth of the claims; (3) the state of the prior art; (4) the predictability or unpredictability of the art; (5) the relative skill of those in the art; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary.

Consideration of the relevant factors sufficient to establish a *prima facie* case for lack of enablement is set forth herein below:

(1) The nature of the invention and (2) the breadth of the claims:

The claims are drawn to compounds of claims 2 and 14, their method of use and their preparation. Thus, the claims taken together with the specification imply these compounds can treat neurokinin-mediated disorders.

(3) The state of the prior art and (4) the predictability or unpredictability of the art:

The elected compound is considered novel. The formation of working prodrugs is unpredictable and requires undue testing. Jantzen (*Modern Pharmaceutics*, **1996**, pages 451 and 596) states "The most serious disadvantage to the prodrug approach to controlled-sustained delivery is that extensive development must be undertake to find the correct chemical modification for a specific drug. Additionally, once a prodrug is formed, it is a new drug entity and, therefore, requires extensive and costly studies to determine safety and efficacy."

(5) The relative skill of those in the art:

One of ordinary skill in the art is a chemist familiar with amide couplings.

(6) The amount of direction or guidance presented and (7) the presence or absence of working examples:

The specification has provided guidance for preparation of compounds described as final compounds and in tables 1-5.

However, the specification does not provide guidance for all possible substitution patterns for rings that are represented by variable R^2.

(8) The quantity of experimentation necessary:

Considering the state of the art as discussed by the references above, particularly with regards to claims 2-3 and 8-9, and the high unpredictability in the art as evidenced therein, and the lack of guidance provided in the specification, one of ordinary skill in the art would be burdened with undue experimentation to practice the invention commensurate in the scope of the claims.

5. Claims 6, 7, and 16 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the *in vitro* testing of the prepared compounds against NK1, NK2, and NK3 receptors, does not reasonably provide enablement for *in vivo* testing of the claimed compounds. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Applicants show that the prepared compounds can bind to NK1, NK2, and NK3 receptors *in vitro*. However, applicants do not show that any of these compounds work as well *in vivo*. Giuseppe et al. (*Expert Opinion on Therapeutic Patents*, **1997**, *7(4)*, 307-323) state that even though compound 6 (page 311) worked well as an *in vitro* compound, it was not a suitable candidate for conducting *in vivo* studies. The reasons it was not considered are: poor pharmacokinetic properties and its peptide nature.

> The factors to be considered in determining whether a disclosure meets the enablement requirements of 35 U.S.C. 112, first paragraph, have been described in *In re Wands*, 858 F.2d 731, 8 USPQ2d 1400 (Fed. Cir., 1988). The court in Wands states, "Enablement is not precluded by the necessity for some experimentation, such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue', not 'experimentation'" (*Wands*, 8 USPQ2sd 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations" (*Wands*, 8 USPQ2d 1404). Among these factors are: (1) the nature of the invention; (2) the breadth of the claims; (3) the state of the prior art; (4) the predictability or unpredictability of the art; (5) the relative skill of those in the art; (6) the

amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary.

Consideration of the relevant factors sufficient to establish a *prima facie* case for lack of enablement is set forth herein below:

(1) The nature of the invention and (2) the breadth of the claims:

The claims are drawn to compounds that can bind to neurokinin receptors. Thus, the claims taken together with the specification imply these compounds can treat disorders mediated by neurokinins.

(3) The state of the prior art and (4) the predictability or unpredictability of the art:

Even though the elected compound is considered novel, there is unpredictability regarding the ability of the compounds to work both *in vitro* and *in vivo*.

(5) The relative skill of those in the art:

One of ordinary skill in the art is a scientist familiar with the execution of binding studies.

(6) The amount of direction or guidance presented and (7) the presence or absence of working examples:

The specification has provided guidance for *in vitro* testing of the prepared compounds.

However, the specification does not provide guidance for the *in vivo* testing of the prepared compounds.

(8) The quantity of experimentation necessary:

Considering the state of the art as discussed by the references above, particularly with regards to claims 6, 7, and 16, and the high unpredictability in the art as evidenced therein, and the lack of guidance provided in the specification, one of ordinary skill in the art would be burdened with undue experimentation to practice the invention commensurate in the scope of the claims.

Double Patenting

6. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

7. Claim 8 is provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claim 1 of copending Application No. 10 / 560476 (filed June 7, 2004). Although the conflicting claims are not identical, they are not patentably distinct from each other because each of the claims is a composition comprising a compound of formula I. Example B2 of 10/560476 is the elected species of the instant application, and hence is embraced by both applications. Although the composition of 10/560476 also contains an opioid analgesic, so could the composition of claim 8 in the instant application.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

8. Claims 2-4 and 8, are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 2-4 and 13-15 of copending Application No. 10/540045 (filed December 17, 2003). Although the conflicting claims are not identical, they are not patentably distinct from each other because example B1 (column 14) of

10/540045 can be embraced by both sets of claims. Claims 2-4 of both applications are almost identical except for the meaning of variable Y in 10/540045. Claim 8 of the instant is equivalent to claim 13 of 10/540045 because both claims are compositions of compounds of claim 1.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claim Objections

9. Claim 14 is objected to because of the following informalities: When R^3 is attached to the nitrogen, the nitrogen is trivalent. Thus the radical group is not always divalent. Appropriate correction is required.

10. Claims 6-10 and 16 are objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Claims 6-10 and 16 are based on withdrawn claim 1.

11. Claim 12 is objected to because of the following informalities: it has no period. Appropriate correction is required.

Allowable Subject Matter

12. No claims are allowed.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Noble Jarrell whose telephone number is (571) 272-9077. The examiner can normally be reached on M-F 7:30 A.M - 6:00 P.M. EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mr. James O. Wilson can be reached on (571) 272-0661. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Noble Jarrell /NJ/

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